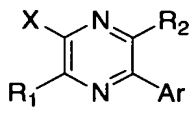
CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



Formula I

or stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms, wherein in formula I,

X is selected from a modified monocyclic group, aryl cycloalkyl, substituted aryl cycloalkyl, heteroaryl cycloalkyl, substituted heteroaryl cycloalkyl, aryl heterocycloalkyl, substituted aryl heterocycloalkyl, heteroaryl heterocycloalkyl, or substituted heteroaryl heterocycloalkyl (point of attachment being either nitrogen or carbon);

modified monocyclic group is selected from cycloalkyl, aryl, heterocycloalkyl, heteroaryl that is substituted with Y or $(CR_bR_b)_nZ$, wherein,

Y is selected from CN, NO_2, C(O) R_a, C(S) R_a, $C(O)OR_a$, $C(S)OR_a$, $C(O)NR_aR_a$, $C(S)NR_aR_a$, $NR_aC(O)R_a$, $NR_aC(S)R_a$, $NR_aC(O)NR_aR_a$, $NR_aC(S)NR_aR_a$, $NR_aC(O)OR_a$, $OC(O)R_a$, OC(S) R_a, $OC(O)NR_aR_a$, $OC(S)NR_aR_a$, $S(O)_mNR_aR_a$, $NR_aS(O)_mR_a$, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, cycloalkyl, substituted cycloalkyl, OR_c, and NHR_c;

Z is selected from Y, OR_a, NR_aR_a, and $S(O)_mR_a$;

R_b is independently selected from H, alkyl, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl optionally substituted with 1-5 Rt;

R_c is selected from aryl, heteroaryl, heterocycloalkyl, or cycloalkyl optionally substituted with 1 to 5 of Rt;

n is selected from 1-6; and

m is selected from 0, 1, and 2;

Ar is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl;

R_1, R_2, are independently selected from H, halogen, $-NO_2$, -CN, $-OR_a$, $-NR_aR_a$, $-C(O)R_a$, $-C(O)NR_aR_a$, $-C(S)NR_aR_a$, $-C(O)OR_a$, $-C(S)OR_a$, $S(O)_mR_a$, $-S(O)_mNR_aR_a$, $-NR_aS(O)_mR_a$, $-NR_aC(O)OR_a$, $-NR_aC(O)R_a$, $-NR_aC(O)NR_aR_a$, $-NR_aC(S)NR_aR_a$, and $-OC(O)NR_aR_a$, $-OC(O)R_a$, $OC(O)OR_a$, CR_bR_bZ, R_f;

R_a is independently selected from H, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl optionally substituted with 1 to 5 of R_t, oxo (=O), thione (=S), phenyl, heteroaryl, or heterocycloalkyl where phenyl, heteroaryl, and heterocycloalkyl are optionally substituted with 1 to 5 independently taken from R_t;

R_f is independently selected from ethyl, propyl, butyl, pentyl, cycloalkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl optionally substituted with 1 to 5 of R_t, oxo (=O), thione (=S), phenyl, heteroaryl, or heterocycloalkyl where phenyl, heteroaryl, and heterocycloalkyl are optionally substituted with 1 to 5 independently taken from R_t;

R_t is independently selected from R_w, halogen, $-NO_2$, $-NR_wR_w$, $-OR_w$, $-SR_w$, -CN, $-C(O)NR_wR_w$, $-C(O)R_w$, $-OC(O)NR_wR_w$, $-OC(O)R_w$, $-NR_wC(O)R_w$, $-NR_wC(O)NR_wR_w$, $-NR_wC(O)OR_w$, $-S(O)_mR_wR_w$, $-NR_wS(O)_mR_w$, $-S(O)_2NR_wR_w$, $-NR_wS(O)_2NR_wR_w$; and

R_w is independently selected from H, alkyl, cycloalkyl, phenyl, benzyl, heteroaryl or heterocycle where phenyl, benzyl, heteroaryl and heterocycloalkyl may be optionally substituted with alkyl or halogen.

2. A compound according to claim 1 wherein, in Formula I, X is a modified monocyclic group.

3. A compound according to claim 2 wherein the modified monocyclic group is pyrrolidine or piperidine substituted with $(CR_bR_b)_nZ$.

4. A compound according to claim 3 wherein the modified monocyclic group is piperidine substituted with $(CR_bR_b)_nZ$ where R_b is hydrogen and n is 1.

5. A compound according to claim 1, which is

2-(2,4-Dichlorophenyl)-3,6-diethyl-5-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]pyrazine;

2-(2-Chloro-4-methoxyphenyl)-3,6-diethyl-5-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]pyrazine;

2-(2,4-dichlorophenyl)-3,6-diethyl-5-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]pyrazine;

2-(2-chloro-4-methoxyphenyl)-3,6-diethyl-5-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]pyrazine;

2-(2-chloro-4-methoxyphenyl)-3,6-diethyl-5-[(3R)-3-(methoxymethyl)pyrrolidin-1-yl]pyrazine;

2-(2-chloro-4-methoxyphenyl)-5-[(3R)-3-(ethoxymethyl)pyrrolidin-1-yl]-3,6-diethylpyrazine;

2-(2-chloro-4-methoxyphenyl)-3,6-diethyl-5-[(3S)-3-(methoxymethyl)pyrrolidin-1-yl]pyrazine;

2-(2-chloro-4-methoxyphenyl)-5-[(3S)-3-(ethoxymethyl)pyrrolidin-1-yl]-3,6-diethylpyrazine;

2-(2-chloro-4-methoxyphenyl)-3,6-diethyl-5-[4-(methoxymethyl)piperidin-1-yl]pyrazine, or

a pharmaceutically acceptable salt of any said compound.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

7. A method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound of claim 1.

8. A method of treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal, comprising administering to the animal a therapeutically effective amount of a compound of claim 1.

9. A method for the treatment of a disorder, the treatment of which can be effected or facilitated by antagonizing CRF, comprising administering to the mammal a therapeutically effective amount of a compound of compound of claim 1.

10. A method for screening for ligands for CRF receptors, which method comprises: a) carrying out a competitive binding assay with a CRF receptor, a compound of claim 1, which is labelled with a detectable label, and a candidate ligand; and b) determining the ability of said candidate ligand to displace said labelled compound.

11. A method for detecting CRF receptors in tissue comprising: a) contacting a compound of claim 1, which is labelled with a detectable label, with a tissue, under conditions that permit binding of the compound to the tissue; and b) detecting the labelled compound bound to the tissue.

12. A method of inhibiting the binding of CRF to a CRF-1 receptor, comprising contacting a compound of claim 1, with cells expressing the CRF1 receptor, wherein the compound is present in the solution at a concentration sufficient to inhibit the binding of CRF to the CRF-1 receptor.

13. The method of claim 12, wherein the cells are IMR32 cells.

14. A compound according to claim 1, wherein the compound exhibits an IC50 for CRF binding of 1 micromolar or less.

15. A compound according to claim 1, wherein the compound exhibits an IC50 for CRF binding of 100 nanomolar or less.

16. A compound according to claim 1, wherein the compound exhibits an IC50 for CRF binding of 10 nanomolar or less in a standard assay of CRF binding.

17. A method of promoting smoking cessation, comprising administering to a patient in need thereof an effective amount of a compound of claim 1.

18. A method of treating a disorder in a human, comprising administering to the human a therapeutically effective amount of a compound of claim 1, wherein the disorder is selected the group consisting of anxiety-related disorders; mood disorders; post-traumatic stress disorder; supranuclear palsy; immune suppression; drug or alcohol withdrawal symptoms; inflammatory disorders; pain; asthma; psoriasis and allergies; phobias; sleep disorders induced by stress; fibromyalgia; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; human immunodeficiency virus infections; neurodegenerative diseases; gastrointestinal diseases; eating disorders; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical

dependencies and addictions; psychosocial dwarfism, hypoglycemia, and skin disorders; and hair loss.

19. A method according to claim 18 wherein the disorder is selected the group consisting of anxiety-related disorders; mood disorders; bipolar disorders; post-traumatic stress disorder; inflammatory disorders; chemical dependencies and addictions; gastrointestinal disorders; and skin disorders.

20. A method according to claim 19 wherein the disorder is selected from anxiety-related disorders and mood.

21. A method according to claim 20 wherein the anxiety-related disorder is generalized anxiety and the mood disorder is depression.